Re: Cancer Risks in BRCA1 Carriers: Time for the Next Generation of Studies

In a recent editorial in the Journal (1), Gruber and Petersen discuss two studies (2,3) that concern risks of cancers other than of the breast or ovary among BRCA1 mutation carriers. These two studies were based on families ascertained because of relatives affected with breast, ovarian, or fallopian tube cancers. Family-based study designs are known to yield overestimates of risk, even with adjustments for ascertainment (4). Gruber and Petersen (1) suggest that cohort studies of BRCA1 carriers are limited by cost, sample size, and ethical considerations and that individual population-based case-control studies of prostate, colorectal, pancreatic, stomach, and other cancers are to be preferred. We believe that the most efficient method for evaluating the role of BRCA1 (or BRCA2) mutations in these cancer types would be to carry out a large population-based study of a cancer site that has both a large proportion of case patients carrying mutations and risk factors unlikely to be shared with the cancer types in question. For these two genes, the optimal site is ovarian cancer, and we have done such a study (5). Ovarian cancer appears not to have any salient genetic, reproductive, or other risk factors in common with breast cancer or with most other cancers (6), and the fraction of case patients with ovarian cancer who carry BRCA1 or BRCA2 mutations, approximately 9%, is larger than that for any other type of cancer in adults. Because these mutations seem to occur only in case patients with invasive nonmucinous ovarian cancer, studies of ovarian cancer restricted to this histologic type would identify an even larger number of carriers, approximately 13% (5).

With regard to the findings of the two studies (2,3) discussed by Gruber and Petersen (1), our study (5) showed no associations between BRCA1 mutations and risks of colorectal or prostate cancer. We did see a statistically significant risk for stomach cancer (relative risk [RR] = 6.2, 95% confidence interval [CI] = 2.0 to 19.0), which occurred only among male first-degree carrier relatives and, therefore, could not have been misdiagnosed ovarian cancer (5).

We also saw a suggestion of an increased risk for pancreatic cancer (RR = 1.5, 95% CI = 0.2 to 11.0), particularly among male relatives under 65 years of age (RR = 5.5, 95% CI = 0.6 to 49.0) (5). Finally, we observed a statistically significantly increased risk of leukemias and lymphomas (RR = 2.6, 95% CI = 1.0 to 6.6) (5). These associations are intriguing but were based on only 649 case probands. It is our intention to extend this work to a much larger sample to generate more precise risk estimates.

Harvey A. Risch
Steven A. Narod

REFERENCES


NOTES

Editor’s note: Drs. Gruber and Petersen declined our invitation to respond.

Affiliations of authors: H. A. Risch, Department of Epidemiology and Public Health, Yale University School of Medicine, New Haven, CT; S. A. Narod, Centre for Research in Women’s Health, Sunnybrook and Women’s College Health Sciences Centre, University of Toronto, Toronto, Ontario, Canada.

Correspondence to: Harvey A. Risch, M.D., Ph.D., Department of Epidemiology and Public Health, Sunnybrook and Women’s College Health Sciences Centre, University of Toronto, Toronto, Ontario, Canada.

Correspondence to: Harvey A. Risch, M.D., Ph.D., Department of Epidemiology and Public Health, Yale University School of Medicine, 60 College St., P.O. Box 208034, New Haven, CT 06520-8034 (e-mail: Harvey.Risch@Yale.edu).